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Abstract: Accumulating evidence suggests a role of FKBP5, a co-chaperone regulating the glucocorticoid receptor sensitivity, in the etiology of depression and anxiety disorders. Based on recent findings of altered amygdala activity following childhood adversity, the present study aimed at clarifying the impact of genetic variation in FKBP5 on threat-related neural activity and coupling as well as morphometric alterations in stress-sensitive brain systems. Functional magnetic resonance imaging during an emotional face-matching task was performed in 153 healthy young adults (66 males) from a high-risk community sample followed since birth. Voxel-based morphometry was applied to study structural alterations and DNA was genotyped for FKBP5 rs1360780. Childhood adversity was measured using retrospective self-report (Childhood Trauma Questionnaire) and by a standardized parent interview assessing childhood family adversity. Depression was assessed by the Beck Depression Inventory. There was a main effect of FKBP5 on the left amygdala, with T homozygotes showing the highest activity, largest volume and increased coupling with the left hippocampus and the orbitofrontal cortex (OFC). Moreover, amygdala-OFC coupling proved to be associated with depression in this genotype. In addition, our results support previous evidence of a gene-environment interaction on right amygdala activity with respect to retrospective assessment of childhood adversity, but clarify that this does not generalize to the prospective assessment. These findings indicated that activity in T homozygotes increased with the level of adversity, whereas the opposite pattern emerged in C homozygotes, with CT individuals being intermediate. The present results point to a functional involvement of FKBP5 in intermediate phenotypes associated with emotional processing, suggesting a possible mechanism for this gene in conferring susceptibility to stress-related disorders.

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ORIGINAL ARTICLE

Role of *FKBP5* in emotion processing: results on amygdala activity, connectivity and volume

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Abstract Accumulating evidence suggests a role of FKBP5, a co-chaperone regulating the glucocorticoid receptor sensitivity, in the etiology of depression and anxiety disorders. Based on recent findings of altered amygdala activity following childhood adversity, the present study aimed at clarifying the impact of genetic variation in *FKBP5* on threat-related neural activity and coupling as well as morphometric alterations in stress-sensitive brain systems. Functional magnetic resonance imaging during an emotional face-matching task was performed in 153 healthy young adults (66 males) from a high-risk community sample followed since birth. Voxel-based morphometry was applied to study structural alterations and DNA was genotyped for *FKBP5* rs1360780. Childhood adversity was measured using retrospective self-report (Childhood Trauma Questionnaire) and by a standardized parent interview assessing childhood family adversity. Depression was assessed by the Beck Depression Inventory. There was a main effect of *FKBP5* on the left amygdala, with T homozygotes showing the highest activity, largest volume and increased coupling with the left hippocampus and the orbitofrontal cortex (OFC). Moreover, amygdala-OFC coupling proved to be associated with depression in this genotype. In addition, our results support previous evidence of a gene-environment interaction on right amygdala activity with respect to retrospective assessment of childhood adversity, but clarify that this does not generalize to the prospective assessment. These findings indicated that activity in T homozygotes increased with the level of adversity, whereas the opposite pattern emerged in C homozygotes, with CT individuals being intermediate. The present results point to a functional involvement of *FKBP5* in intermediate phenotypes associated with emotional processing, suggesting a possible

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mechanism for this gene in conferring susceptibility to stress-related disorders.

Keywords *FKBP5* · Childhood adversity · Amygdala · fMRI · Connectivity · Voxel-based morphometry

Introduction

Mood and anxiety disorders are the most common mental health disorders, with estimated 12-month prevalence rates of up to 14 % in Europe (Wittchen et al. 2011). Altered neural affective processing is considered a major biological risk factor for such disorders. Research has revealed the amygdala to be a core region of emotion processing, suggesting heightened amygdala activity as a possible neural mechanism underlying mood and anxiety disorders (Drevets et al. 2008; e.g., Etkin and Wager 2007; Siegle et al. 2007). To identify risk markers which lead to enhanced amygdala activity and, in general, altered emotion processing may thus be of high scientific and clinical relevance.

The amygdala is involved in the regulation of the stress response, presumably through excitatory effects on the hypothalamus-pituitary axis (HPA) (Feldman and Weidenfeld 1998). A special role in mediating stress reactivity is played by the glucocorticoid receptor (GR), which is densely expressed in the amygdala (Johnson et al. 2005). The GR is the major target of the stress hormone cortisol and is preferentially activated when high levels of cortisol are circulating (Reul and de Kloet 1985). Variation in GR sensitivity may thus lead to a maladaptive stress response and provide a vulnerability factor for stress-related diseases (Anacker et al. 2011; Hauger et al. 2012). There is ample evidence of genetic variation affecting GR-mediated regulation of the stress response. A promising candidate gene is *FKBP5,* which codes for a protein FK506 binding protein 5-51, a co-chaperone of the hsp90, and regulates the affinity of the GR for cortisol (Binder 2009; Denny et al. 2000; Wochnik et al. 2005). Recently, a strong stress-induced increase of *FKBP5* mRNA in the central amygdala has been demonstrated (Scharf et al. 2011), supporting the significance of FKBP5 regulation during central GR activation. One of the most commonly investigated polymorphisms in this gene is rs1360780, a single nucleotide polymorphism (SNP) located in intron two at chromosome six (position 6p21.31) with a minor allele frequency of 42 % (Binder et al. 2008). Its functional relevance has been linked to higher *FKBP5* expression in human blood monocytes in TT compared to C allele carriers (Binder et al. 2004). In healthy T allele carriers (unlike in those with PTSD symptoms), less dexamethasone suppression has been demonstrated which might be indicative of GR resistance (Binder et al. 2008). This, in turn, leads to less effective negative feedback which would normally be induced by binding of cortisol on the GR, resulting in a prolonged stress response following stress exposure. Indeed, T homozygotes were found to exhibit elevated cortisol levels during recovery after stress (Ising et al. 2008). In line with this, rs1360780 has been associated with psychopathology such as mood disorders (Binder et al. 2004; Lavebratt et al. 2010; Lekman et al. 2008; Zobel et al. 2010) and suicidality (Brent et al. 2010). Moreover, this SNP has been shown to interact with childhood abuse in predicting PTSD symptoms (Binder et al. 2008) and susceptibility to depression (Appel et al. 2011), with an increased risk in the TT genotype following childhood abuse.

Since genetic associations with behavioral phenotypes have often been inconclusive due to their complexity, the study of endophenotypes, which may be more sensitive to genetic variation, has been suggested as a promising approach (Gottesman and Gould 2003; Meyer-Lindenberg and Weinberger 2006; Rasch et al. 2010a). Considering *FKBP5*, recent evidence indicates that rs1360780 interacts with childhood adversity to predict amygdala activity in adolescents (White et al. 2012). While in T homozygotes, activity in the right amygdala increased with the level of emotional neglect (EN), no such effect was observed in C homozygotes. Emotional neglect was assessed retrospectively using a subscale of the Childhood Trauma Questionnaire (CTQ, Bernstein et al. 2003). In addition to the effect on amygdala activity, *FKBP5* has been related to increased hippocampal activity as well as to differences in hippocampal shape (Fani et al. 2013), volume (Zobel et al. 2010) and volume change with behavioral trauma treatment (Levy-Gigi et al. 2013). No study, so far, has investigated the impact of *FKBP5* on amygdala volume. However this issue may be crucial, given the facts that *FKBP5* is expressed in the amygdala (Scharf et al. 2011) and that amygdala volume is increased following stress (Buss et al. 2012; Lupien et al. 2011; Tottenham et al. 2010).

To restrict analyses to amygdala activity only, would be insufficient in the view of the human brain as a complex network of interacting cell populations. Altered connectivity patterns have been suggested to represent important endophenotypes of psychiatric disorders (Tost et al. 2012). Both PTSD and depression, characterized by altered emotional processing and memory, have been linked to *FKBP5*. With regard to emotional processing, the orbitofrontal cortex has been implicated in the processing and integration of emotional material (Rolls and Grabenhorst 2008) with structural (Cavada et al. 2000) as well as functional (Schoenbaum et al. 2000) connections to the amygdala. In addition, OFC activation has been shown to

be increased during emotion regulation (Ochsner et al. 2004). Previous studies investigating amygdala-OFC connectivity have provided evidence for both reduced (Meyer-Lindenberg et al. 2005, 2006) and increased coupling (Drabant et al. 2006; Rasch et al. 2010b) in groups at risk. The amygdala-hippocampus connection has been demonstrated to be critically involved in the formation of emotional memory (Hooker et al. 2008; Phelps 2004). Moreover, amygdala-hippocampus connectivity has been shown to be influenced by stress exposure (Ghosh et al. 2013; Vaisvaser et al. 2013).

Given the current paucity of imaging results, the present study aimed at clarifying the role of *FKBP5* rs1360780 in affecting amygdala activity by investigating (1) a genetic main effect of *FKBP5* and (2) a possible interaction of *FKBP5* with childhood adversity. Critically, the present study extends previous work: first, by providing measures of childhood adversity drawn from both retrospective self-report (Childhood Trauma Questionnaire, CTQ) and prospectively ascertained objective information on childhood family adversity (CFA) collected in young adults from a longitudinal study. While the CTQ assesses memories of different types of childhood maltreatment, CFA covers qualitatively different stressors, which do not address maltreatment directly, but pertain to more adverse family circumstances such as marital discord or early parenthood. Given the role of the amygdala in emotional memory, we expected to find greater effects with regard to the CTQ, which has previously been related to emotional memory reactivation (Polanczyk et al. 2009). Second, we extended previous work by investigating connectivity patterns and volumetric differences in the amygdala. As the TT genotype has been associated with a prolonged cortisol response after stress and an increased risk for stress-related disorders (Binder 2009), we expected (1) increased amygdala-hippocampus connectivity, (2) altered (reduced or increased) amygdala-OFC coupling and (3) increased amygdala volume in T homozygotes. Third, we contributed to the literature by examining whether a possible effect on amygdala-OFC coupling was related to depression. Previous research has shown that impaired connectivity between the amygdala and key regions of emotion processing rather than enhanced amygdala activation increased the risk of anxiety disorders and depression (Buckholtz et al. 2008; Pezawas et al. 2005).

Materials and methods

Sample

This investigation was conducted in the framework of the Mannheim Study of Children at Risk, an ongoing epidemiological cohort study of the long-term outcome of early risk factors (Laucht et al. 1997, 2000). Assessments were performed at the age of 3 months and at regular intervals throughout development until young adulthood. At the age of 25, a subsample of $N = 181$ healthy, right-handed individuals of European descent participated in an fMRI session investigating affective processing. Exclusion criteria were usual contraindications for MRI (such as heart pacemaker, neurological abnormalities, history of seizures, unconsciousness or head trauma) current psychiatric disorders, and psychotropic medication. For $N = 155$ participants, information on *FKBP5* genotype was available. From this sample, two participants were excluded due to movement artifacts (>2 mm) and systemic lupus erythematosus, respectively, resulting in a final sample of $N = 153$ individuals (66 males, 87 females). The study was approved by the ethics committee of the University of Heidelberg and written informed consent was obtained from all participants.

Psychological assessments

Exposure to childhood adversity was assessed in two ways. First, a prospective measure of childhood family adversity (CFA) according to an 'enriched' family adversity index as proposed by Rutter and Quinton (1977) was derived from a standardized parent interview conducted at each assessment during childhood. The index measures the presence of 11 adverse family factors, covering characteristics of the parents, the partnership, and the family environment during a period of 1 year prior to the assessment (Laucht et al. 1997) (for details, see Online Resource 1). A total childhood family adversity score was calculated by counting the number of factors present in 5 assessment points at the ages of 3 months, 2, 4, 8 and 11 years. Data were provided from all participants at each assessment.

Second, at the age of 23, participants completed the brief screening version of the Childhood Trauma Questionnaire (CTQ, Bernstein et al. 2003). The CTQ entails a retrospective assessment of five types of self-reported childhood maltreatment, i.e., sexual, physical, and emotional abuse, and emotional and physical neglect. Good psychometric properties have been confirmed for the German version (Wingenfeld et al. 2010). The CTQ yields a total score and subscale scores for each type of maltreatment. Based on previous research (e.g., White et al. 2012), we focused on the subscale of emotional neglect (EN) and, additionally, included the total score.

At the age of 25, the Structured Clinical Interview for DSM-IV (SCID-I German version Wittchen et al. 1997) was administered to assess psychiatric disorders in the young adults. To examine current drug use, participants completed a substance use inventory (Müller and Abbet

1991). On the day of the experiment, they were asked about any use of current medication.

Depressive symptoms were assessed with the Beck Depression Inventory [BDI, German version by Hautzinger et al. (1994)] at age 25 years. In addition, to obtain a more stable measure of depression a composite score of the BDI levels during adulthood (ages 19, 22, 23 and 25 years) was formed. The number of symptoms present at each assessment, available for $N = 151$ individuals, was z-transformed and summed up to a total score.

fMRI face-matching task

A face-matching task which robustly activates the amygdala was administered (Hariri et al. 2002). For 12 blocks, sequences of fearful/angry faces were alternated with sequences of shapes. At the beginning of each block, a short instruction ("comparison faces", "comparison shapes") was shown on the screen for 2 s. In the face blocks, trios of faces derived from the Ekman and Friesen (1979) stimulus set, balanced for gender and emotional expression, were presented. Participants were instructed to indicate which of the two faces at the bottom was identical to the target face (on top) and to press the button on the respective side. In the sensorimotor control task, participants had to compare circles and ellipses according to the same criterion. Both stimulus sets consisted of six different trios of faces or shapes and were presented on average every 2.5 s (slightly jittered in 12 different steps to vary by 0–50 ms around the mean). Finally, an end screen was shown for 8 s. The total task time was 409 s. Reaction time and accuracy were measured.

fMRI parameters and data analysis

Functional magnetic resonance imaging was performed using a 3 T scanner (Magnetom TRIO, Siemens, Erlangen, Germany) with a standard 12-channel head coil. The imaging protocol consisted of a localizer scan followed by a BOLD-sensitive T2*-weighted echoplanar imaging sequence and a structural T1-weighted sequence. For functional imaging, a total of 183 volumes with 36 slices (matrix 64×64, resolution $3.43 \times 3.43 \times 3$ mm with 1 mm gap, repetition time = 2210 ms, echo time = 28 ms, flip angle = 90°) covering the whole brain were acquired. The slices were inclined 20° from the anterior/posterior commissure level in order to minimize dropout artifacts in orbitofrontal and mediotemporal regions. The first four images were discarded to allow longitudinal magnetization to reach equilibrium. The functional images were analyzed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.12. (Mathworks Inc., Natick, MA, USA). Preprocessing included slice time correction of the volumes to the first slice, realignment to correct for movement artifacts, coregistration of functional and anatomical data, spatial normalization to standard MNI space (Montreal Neurological Institute), and smoothing with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM). Two vectors comprising onsets and durations of either shapes or faces were convolved with the SPM8 canonical hemodynamic response function in the context of a General Linear Model in order to model the BOLD time course. A further six movement parameters were included as regressors of no interest.

First-level contrast images of faces > shapes activation were entered into a second-level group analysis. To account for genotype and childhood adversity effects, *FKBP5* (1 = CC, 2 = CT, 3 = TT) and the continuous adversity measures CFA (range 0–10), CTQ total (range 25–63) and CTQ EN (range 5–20) were added separately as covariates. The interaction effect was investigated by including the interaction term, which is the multiplication of the two covariates (*FKBP5* × adversity). The covariates were mean-centered and the results were controlled for gender. For exploratory, whole-brain analyses, an uncorrected threshold of $p < .001$ and a criterion of five adjacent voxels was set. According to previous research, the bilateral amygdala was defined as a region of interest (ROI) using the Brodmann mask implemented in the WFU PickAtlas v2.4 (Maldjian et al. 2003). To correct for multiple comparisons, a $p < .05$ family-wise error (FWE) correction was applied. Post-hoc *t* tests were carried out to examine group differences. To visualize and further analyze the main and interaction effects, mean contrast values of each participant were extracted from the significant cluster in the left amygdala and exported to SPSS Statistics 20 (IBM, Armonk, NY).

Functional connectivity

Psychophysiological interaction (PPI) analysis was performed to reveal the task-related covariation of activation in a seed region with the whole brain (Friston et al. 1997). To further elucidate brain mechanisms associated with the exaggerated amygdala responses, 4 mm spheres around the peak activation in the left amygdala (MNI $x = -22$, $y = -8$, $z = -12$) and the right amygdala (MNI $x = 22$, $y = -8$, $z = -12$) identified in the contrast faces > shapes were used corresponding to the gene and the interaction effect, respectively. The time course of activation in these regions was extracted, high-pass-filtered and deconvolved, representing the first regressor (physiological variable) in the PPI analysis. As the second regressor, the experimental condition (faces > shapes) was entered. The regressor of interest was the PPI term, defined as the cross product of the time series of the seed region and the experimental condition. To account for genotype, environmental and

gene-environment effects, the PPI contrast images were entered into a second-level random-effects analysis using the same covariates previously mentioned in the activation analysis. Regions of interest were the orbitofrontal cortex and the hippocampus defined by the WFU PickAtlas version 2.4 (Maldjian et al. 2003). FWE correction was applied in the ROIs ($p_{FWE} < .05$). Whole-brain results are displayed at $p = .001$ (uncorrected) with a minimum of five adjacent voxels. Pearson correlations were computed to examine the relationship between the significant cluster of amygdala-OFC connectivity and the BDI.

Voxel-based morphometry (VBM)

To further elucidate the functional effect of *FKBP5* on amygdala, we additionally analyzed possible gene and interaction effects on amygdala volume. Therefore, we acquired 1 × 1 × 1 mm T1-weighted anatomical images with 192 slices covering the whole brain (matrix 256 × 256, repetition time = 2300 ms, echo time = 3.03 ms, 50 % distance factor, field of view 256 × 256 × 192 mm, flip angle 9°). Images were bias-corrected and classified into gray matter, white matter, cerebrospinal fluid and non-brain tissue using Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) registration toolbox (Ashburner 2007). An average template from the data was created to which the images were registered. Additionally, the images were affine-transformed to MNI space and smoothed with a 6-mm FWHM kernel. For group statistics of gray matter images, the same analysis strategies as in the functional analysis were performed using SPM8. Total intracranial volume was calculated by adding the tissue probabilities of gray matter, white matter and cerebrospinal fluid and included as an additional covariate. Separate left and right amygdala masks for investigating the gene and interaction effects, respectively, derived from the WFU PickAtlas version 2.4 (Maldjian et al. 2003) were used as ROIs, where FWE correction was applied with a threshold of $p_{FWE} < .05$.

Genotyping

Genomic DNA was prepared from whole blood or saliva according to standard procedures. *FKBP5* rs1360780 was genotyped using a pre-designed TaqMan 5′ nuclease SNP genotyping assay (Life Technologies, USA). Accuracy was assessed by duplicating 15 % of the original sample, and reproducibility was 100 %. Genotype frequencies were CC = 71, CT = 69, and TT = 13, which is in accordance with Hardy–Weinberg equilibrium ($Chi^2 = .44$, $p = .51$).

Results

fMRI

Genotypes were unrelated to gender, task accuracy, reaction time, CTQ total, CTQ EN, childhood family adversity (CFA), years in school, family status and depression (Table 1). In accordance with previous research, a strong bilateral amygdala activation due to the emotional task emerged [left: t (152) = 20.08, $p_{FWE} < .001$, peak voxel: $x = -22$, $y = -8$, $z = -12$, right: t (152) = 21.59, $p_{FWE} < .001$, peak voxel: $x = 22$, $y = -8$, $z = -12$] (whole-brain activation is provided in the Online Resource 2). Adversity measures were significantly correlated (CTQ total and EN with CFA: $r = .341$, $p < .001$, and $r = .325$, $p < .001$, respectively). For the contrast of faces > shapes, there was an effect of *FKBP5* rs1360780 on activity in the left amygdala [$t(150) = 3.17$, $p_{FWE} = .033$, peak voxel: $x = -20$, $y = -10$, $z = -10$]. Post-hoc t tests showed a significantly higher activation in the TT compared to C allele carriers [TT > CC: $t(82) = 3.59$, $p_{FWE} = .013$; TT > CT: $t(80) = 3.29$, $p_{FWE} = .029$], with no significant difference between the latter genotype groups [CT > CC: $t(138) = 1.32$, $p_{uncorr} > .05$; Fig. 1]. In addition, an effect on the right amygdala was found, although it did not survive correction for multiple comparison [$t(150) = 2.89$, $p_{uncorr} = .002$, peak voxel: $x = 30$, $y = -4$, $z = -18$]. Whole-brain activations as a function of *FKBP5* are provided in Online Resource 3. No effects of childhood adversity measures on amygdala activity did survive FWE correction (all $p_{FWE} > .07$, see Online Resource 3; whole-brain activation as a function of adversity is depicted in Online Resource 4).

The *FKBP5* × CTQ EN interaction revealed a significant effect in the right amygdala [$t(148) = 3.01$, $p_{FWE} = .049$, peak voxel: $x = 26$, $y = 2$, $z = -18$]. In detail, amygdala activity in C homozygotes significantly decreased with the level of EN, while in the CT and TT group, activity increased (see Fig. 2). Similar patterns of interaction were obtained for the CTQ total and the CFA measures, but did not survive correction for multiple comparison [CTQ total: $t(148) = 2.19$, $p_{uncorr} = .015$, CFA: $t(148) = 2.09$, $p_{uncorr} = .019$]. Additional information on whole-brain activation for all interactions is provided in Online Resource 5.

Functional connectivity

Analyses revealed a significant effect of *FKBP5* on the connectivity between the left amygdala and the orbitofrontal cortex [left: $t(150) = 3.86$, $p_{FWE} = .010$, $x = -46, y = 40, z = -10$, right: $t(150) = 3.84, p_{FWE} = .015$, $x = 44$, $y = 34$, $z = -4$], indicating increased positive

Table 1 Sample characteristics by *FKBP5* rs1360780 genotype

FKBP5 rs1360780 genotype	CC	CT	TT	*p* value
	71	69	13	.51[a]
Males *N* (%)	32 (45.1)	30 (43.5)	4 (30.8)	.63[a]
Years in school *M* (SEM)	11.69 (.19)	11.83 (.19)	11.92 (.44)	.83[b]
Family status: unmarried *N (%)*	67 (94.4)	67 (97.1)	12 (92.3)	.63[a]
Reaction time faces in ms *M* (SEM)	859.32 (17.99)	882.74 (18.24)	872.65 (42.03)	.66[b]
Reaction time shapes in ms *M* (SEM)	741.04 (13.55)	763.98 (13.75)	730.81 (31.67)	.40[b]
% correct faces *M* (SEM)	97.93 (.34)	97.36 (.35)	97.54 (.80)	.51[b]
% correct shapes *M* (SEM)	96.19 (.38)	95.95 (.38)	95.73 (.89)	.85[b]
CTQ total *M* (SEM)	29.31 (.74)	29.93 (.75)	30.62 (1.72)	.72[b]
CTQ emotional neglect *M* (SEM)	7.43 (.34)	7.77 (.35)	8.00 (.80)	.66[b]
Childhood family adversity (CFA) *M* (SEM)	3.65 (.29)	3.68 (.30)	3.01 (.69)	.71[b]
Beck Depression Inventory (BDI) *M* (SEM)[c]	3.71 (.36)	3.47 (.35)	3.08 (.77)	.73[b]

M mean, *SEM* standard error

[a] Chi^2 test

[b] ANOVA

[c] $p = .24$ for composite score of BDI levels during adulthood $N = 151$)

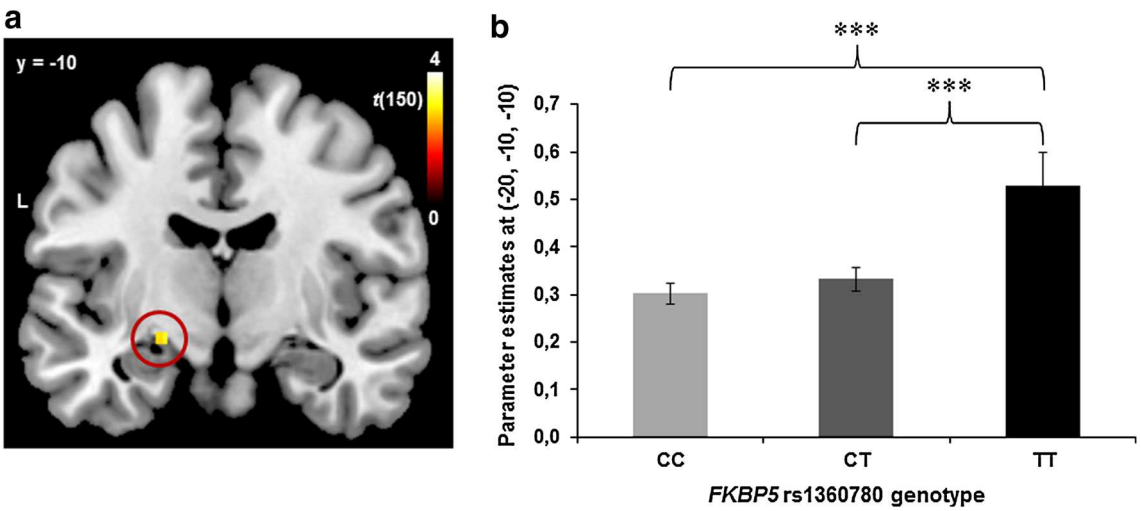

Fig. 1 *FKBP5* genotype-dependent amygdala activation. **a** Activity in the left amygdala in response to emotional faces increased with the number of T alleles ($p_{FWE} = .033$, displayed at $p_{FWE} < .05$ corrected in the ROI). **b** Parameter estimates at the peak voxel in the left amygdala by *FKBP5* genotype (Mean ± SEM are indicated, $***p < .001$ for pairwise comparisons)

coupling in T homozygotes compared to the CT [left: $t(80) = 1.96$, $p_{uncorr} = .026$, right: $t(80) = 2.55$, $p_{uncorr} = .006$] and CC group [left: $t(82) = 2.65$, $p_{uncorr} = .005$, right: $t(82) = 3.46$, $p_{uncorr} < .001$], and between the latter [left: $t(138) = 4.33$, $p_{FWE} = .01$, right: $t(138) = 2.93$, $p_{uncorr} = .002$] (see Fig. 3a). Likewise, an *FKBP5* effect emerged with the left hippocampus [$t(150) = 3.59$, $p_{FWE} = .023$, $x = -32$, $y = -8$, $z = -18$] and, at a trend level, with the right hippocampus [$t(150) = 3.15$, $p_{FWE} = .078$, $x = 26$, $y = -8$, $z = -18$]. Post-hoc *t* tests showed that T homozygotes exhibited higher positive coupling between the left amygdala and the left hippocampus than CT heterozygotes [right: $t(80) = 2.76$, $p_{uncorr} = .004$, left: $t(80) = 2.01$, $p_{uncorr} = .23$] and C homozygotes [left: $t(82) = 2.65$, $p_{uncorr} = .005$, right: $t(82) = 3.31$, $p_{uncorr} = .001$] (see Fig. 3c). In addition, a significant difference between the CT and CC group was obtained for the left [$t(138) = 2.69$, $p_{uncorr} = .004$] and right hippocampus [$t(138) = 2.10$, $p_{uncorr} = .018$]. Information on whole-brain connectivity independent and dependent of genotype is provided in Online Resources 6 and 7. There

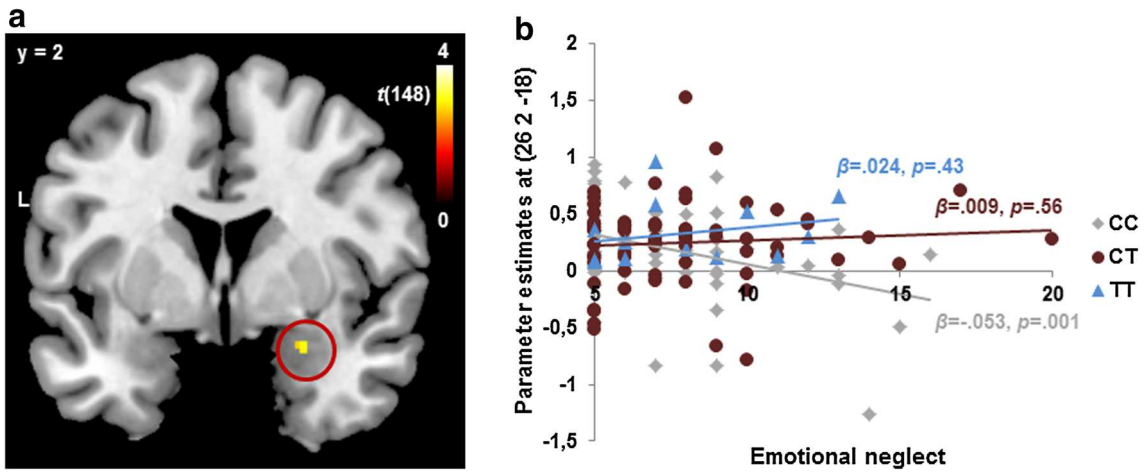

Fig. 2 Interaction between *FKBP5* genotype and EN on right amygdala activity. **a** Activity in the right amygdala increased with the level of EN in T allele carriers, whereas the inverse effect was found in C homozygotes [$t(148) = 3.01$, $p_{FWE} < .05$, displayed at $p_{FWE} < .05$ corrected in the ROI]. **b** Parameter estimates at the peak voxel in the right amygdala for the three genotype groups depending on EN

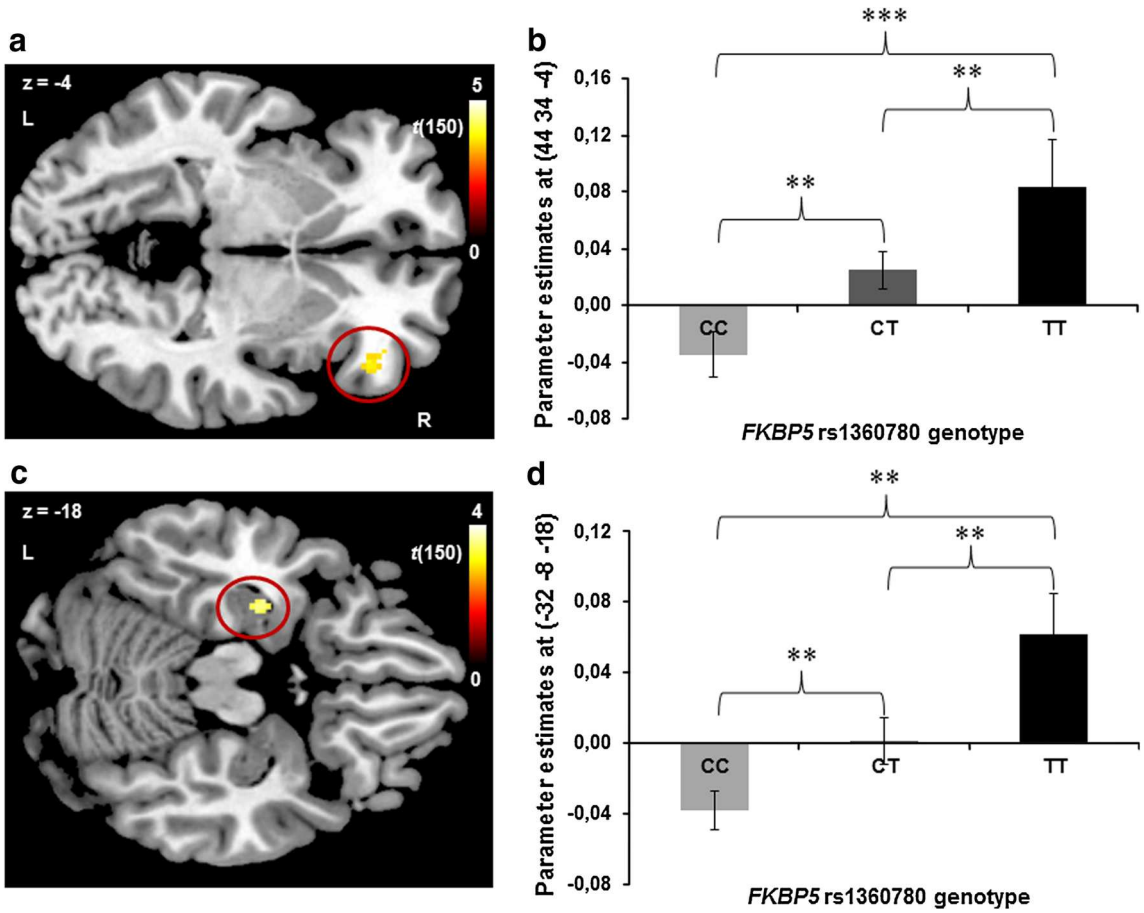

Fig. 3 *FKBP5* genotype-dependent amygdala-orbitofrontal cortex and amygdala-hippocampus connectivity. **a** Coupling between left amygdala and right orbitofrontal cortex in response to emotional faces increased with the number of T alleles ($p_{FWE} = .015$, displayed at $p_{FWE} < .05$ corrected in the ROI). **b** Parameter estimates for the genotype-dependent difference in connectivity. **c** Coupling between left amygdala and left hippocampus in response to emotional faces increased with the number of T alleles ($p_{FWE} = .023$, displayed at $p_{FWE} < .05$ corrected in the ROI). **d** Parameter estimates for the genotype-dependent differences in connectivity (Mean ± SEM are indicated, $^{**}p < .01$, $^{***}p < .001$ for pairwise comparisons)

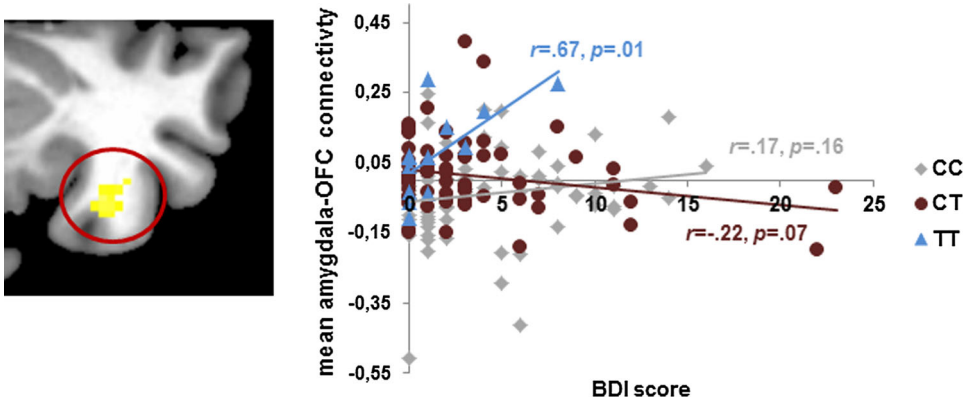

Fig. 4 Scatter plot of the genotype-specific correlation between the significant cluster of amygdala-OFC connectivity and BDI score

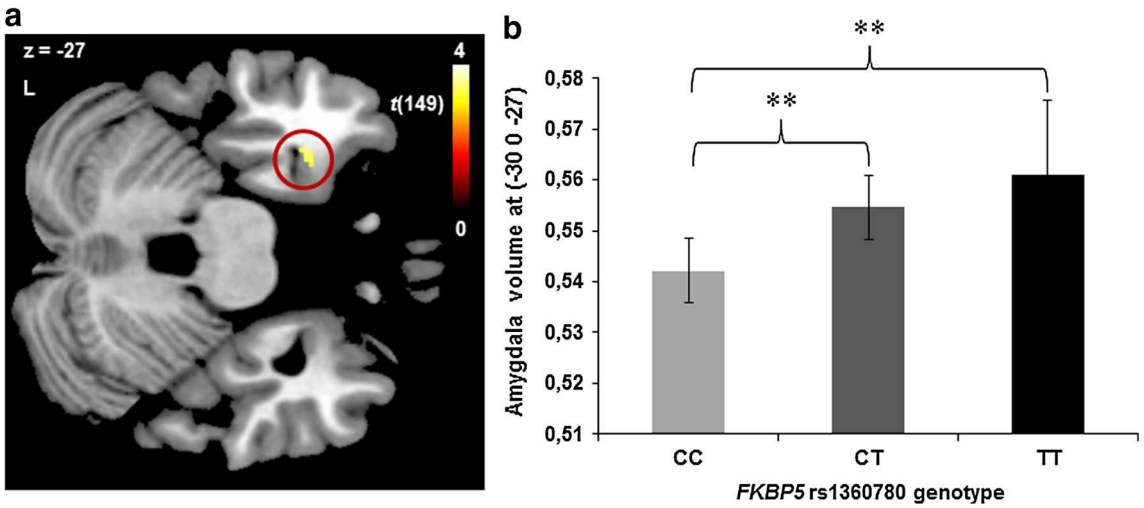

Fig. 5 *FKBP5* genotype-dependent amygdala volume. **a** Volume in the left amygdala increased with the number of T alleles ($p_{FWE} = .024$, displayed at $p_{FWE} < .05$ corrected in the ROI). **b** Amygdala volume in the left amygdala by *FKBP5* genotype (Mean ± SEM are indicated, $^{**}p < .01$ for pairwise comparisons)

were no regions for which connectivity was highest in C homozygotes.

For the interaction between *FKBP5* and CTQ EN, amygdala-hippocampus coupling was significant at a more liberal threshold, but did not survive small volume correction [right: $t(148) = 2.63$, $p_{uncorr} = .005$, $x = 32$, $y = -8$, $z = -16$). As expected, connectivity decreased with EN in C homozygotes and increased in T homozygotes, with the CT heterozygotes being intermediate. Furthermore, no significant interaction effects between *FKBP5* and childhood adversity on the connectivity between the regions of interest were observed (all $p_{FWE} > .25$, for whole-brain connectivity see Online Resource 8).

Association with BDI

A significant genotype-specific correlation between current BDI score and amygdala-OFC connectivity emerged in the TT genotype ($r = .67$, $p = .01$, Fig. 4) suggesting that connectivity increased with the level of depression. While the correlation with the BDI reached trend level in the CT group ($r = -.22$, $p = .07$), it was far from being significant in the CC group ($r = .17$, $p = .16$). A significant correlation in T homozygotes was also obtained using the composite adulthood BDI scores (see Online Resource 3). Using the BDI as an additional covariate in the activity and the connectivity analyses did not change the results (see Online Resource 3).

VBM

The region of interest analysis in the left amygdala revealed an effect of *FKBP5* [$t(149) = 3.49$, $p_{FWE} = .024$, $x = -30$, $y = 0$, $z = -27$]. Specifically, T homozygotes had a significantly increased volume compared to C allele carriers [TT > CC: $t(80) = 2.62$, $p_{uncorr} = .005$; CT > CC: $t(136) = 2.45$, $p_{uncorr} = .008$, Fig. 5]. Regarding the interaction of *FKBP5* with childhood adversity, no voxels in the right amygdala survived cluster threshold (all $p_{uncorr} > .015$).

Discussion

The present study investigated the impact of genetic variation in *FKBP5* on functional and structural characteristics of threat-responsive limbic and corticolimbic circuits. Our findings indicated that T homozygotes showed greater activity in the left amygdala in response to negative emotional faces and a larger amygdala volume than carriers of the C allele. Moreover, this differential amygdala activity was accompanied by an increased coupling to the left hippocampus and to the orbitofrontal cortex in a gene dose-dependent manner, with the amygdala-OFC coupling being associated with depression in T homozygotes. In addition, a gene-environment interaction was observed, suggesting that in T homozygotes, right amygdala activity increased with the level of childhood adversity (EN), whereas the opposite pattern emerged in C homozygotes.

The amygdala has been attributed a central role in processing ambiguity (Davis and Whalen 2001), novelty, and threat (LeDoux 2000), thereby affecting neuroendocrine and autonomic responses. Exaggerated amygdala activation has been suggested to represent a common neurobiological pathway for stress-related disorders, such as depression and anxiety disorders (Drevets et al. 2008; Etkin and Wager 2007). Likewise, in the majority of studies, larger amygdala volumes have been observed in depression (Altshuler et al. 1998; Bremner et al. 2000; Lange and Irle 2004; Tebartz van Elst et al. 1999; van Eijndhoven et al. 2009; Vassilopoulou et al. 2013), (but see Hastings et al. 2004; von Gunten et al. 2000 for opposite findings) and PTSD (Kuo et al. 2012; but see Morey et al. 2012). As T allele carriers are assumed to exhibit a higher expression of *FKBP5* and, thereby, a slower cortisol recovery after challenge, the observed effect on amygdala activity and volume may be related to enhanced cortisol levels. In support of this notion, several neuroimaging studies have strengthened the assumption of a close connection between neural activation in core regions of emotion processing and HPA axis regulation (Root et al. 2009; Taylor et al. 2008; van Stegeren et al. 2008). Similarly, elevated glucocorticoid levels have been associated with larger amygdala volumes (Buss et al. 2012; Lupien et al. 2011). Considering a heightened amygdala response and a larger volume as possible endophenotypes for stress-related disorders, the present findings are in line with previous reports suggesting an important role of the *FKBP5* T allele in mood disorders (Appel et al. 2011; Binder et al. 2004; Lavebratt et al. 2010; Lekman et al. 2008; Zobel et al. 2010) and PTSD (Binder et al. 2008).

The present study is in accordance with a recent finding demonstrating a G × E interaction of *FKBP5* with EN on amygdala activity (White et al. 2012). In both our study and that of White et al. (2012), homozygotes for the rs1360780 T allele showed increasing activity in the right amygdala with the level of childhood neglect, while C homozygotes exhibited decreasing activity, with heterozygotes being intermediate. However, in contrast to White et al. (2012), who found a significant increase in T homozygotes, a significant decrease in C homozygotes was obtained in our study. Several reasons may be responsible for this discrepancy, such as differences in sample composition, reported level of EN, and implementation of the imaging paradigm employed. Moreover, in our study, a prospectively ascertained objective measure of childhood adversity was included, while this was not the case in the White et al. (2012) study. In contrast to the retrospective CTQ self-report, this measure yielded only weak effects on amygdala activity and connectivity. Notably, these measures of stress exposure cover different types of stressors, i.e., emotionally loaded, memorable maltreatment versus objective adverse family conditions. Likewise, the CTQ taps negative events during childhood and adolescence, whereas CFA refers to the first 11 years of life. Similar discrepant G × E findings involving the CTQ and objective measures of childhood adversity have previously been reported (Laucht et al. 2012; Polanczyk et al. 2009). These authors suggested that, instead of the objective occurrence of adverse events, the emotional memories associated with adversity may be important in a gene by adversity interaction with regard to depression. While the CTQ might more specifically identify individuals who have sustained memories with negative emotional content, thus conferring a higher risk for stress-related disorders (Polanczyk et al. 2009; Laucht et al. 2012; Kounou et al. 2013; Huang et al. 2012; Carey et al. 2008; Sarchiapone et al. 2007; Roy 1999; Buchmann et al. 2013), objective measures of adversity may be rather unaffected by memory effects, as they may comprise adverse events which were not recalled (Polanczyk et al. 2009). Although the role of *FKBP5* in emotional memory formation has yet to be elucidated, one could hypothesize that, based on the facilitating role of cortisol on memory formation but not on recall (de Quervain et al. 1998, 2009; Roozendaal 2000; Roozendaal and McGaugh 1997), T homozygotes, assumed to have a prolonged cortisol release, would show an increased consolidation of emotional memories. In line with this, we found an interaction between *FKBP5* and EN on amygdala-hippocampus coupling, indicating increasing connectivity in T homozygotes with the level of adversity and the opposite pattern seen in C homozygotes. However, caution is warranted with this interpretation, as this result failed to exceed FWE correction.

In further support of a possible role of *FKBP5* in emotional memory, T homozygotes were found to exhibit an increased coupling between the amygdala and the hippocampus. Previous research has shown that the amygdala

influences emotional memory formation through connections to the hippocampus (Phelps 2004). Animal studies have demonstrated that amygdala stimulation facilitates hippocampal-dependent learning (Ikegaya et al. 1996; Packard et al. 1994). The enhancing effect of amygdala activity on emotional memory consolidation is a well-established finding in the imaging literature relating activity in the amygdala to later retrieval success (Cahill et al. 1996; Canli et al. 2000; Dolcos et al. 2004, 2005; Hamann et al. 1999; rev: LaBar and Cabeza 2006). In addition, negative memory biases are often found in stress-related disorders (e.g., Bradley et al. 1996; Ridout et al. 2009; Watkins et al. 1992). In accordance with this, depressed patients were found to show an increased coupling between the amygdala and the hippocampus during encoding of negative emotional stimuli, presenting a possible explanation for the increased negative emotional memory (Hamilton and Gotlib 2008). Hence, differential connectivity patterns between the amygdala and the hippocampus may provide a neural model underlying the increased risk of stress-related disorders in T homozygotes. Crucially, this coupling has been demonstrated to increase after stress (Ghosh et al. 2013; Vaisvaser et al. 2013), which is in line with the prolonged stress response in T homozygotes (Binder 2009).

Moreover, the orbitofrontal cortex has been established as one of the major control regions (Konishi et al. 1999) involved in the integration of emotion with goal-directed behavior (Rolls and Grabenhorst 2008; Torregrossa et al. 2008). Its lateral part has been associated with response inhibition (Aron et al. 2004) and emotion regulation (Kanske et al. 2011; Levesque et al. 2003; Lieberman et al. 2007; Meyer-Lindenberg et al. 2005; Ochsner et al. 2004). The observed increased coupling between the amygdala and the orbitofrontal cortex in T homozygotes may reflect an enhanced "excitatory" input from the amygdala to the OFC, indicative of increased sensitivity to emotional stimuli. This pattern might indicate enhanced regulation which is not per se a deficit. However, when confronted with more stressful situations, the capacity to effectively regulate might be compromised in this genotype group, such as by reaching an earlier saturation state, which could increase the risk of stress-related disorders. In line with this suggestion, increased amygdala-OFC coupling has been associated with higher levels of depression in this genotype. Likewise, evidence has been provided of the coupling between amygdala and a regulatory prefrontal region (mPFC) as being meditated by cortisol during resting state (Veer et al. 2012) and fearful face processing (Henckens et al. 2010), highlighting the influence of glucocorticoids on regulatory emotion networks. Previous research has emphasized the role of the anterior cingulate (ACC) in anxiety (Etkin and Wager 2007) and mood disorders (Drevets et al. 2008). Typically, hypoactivation as well as volume decreases and alterations in functional connectivity between the amygdala and the ACC (Anand et al. 2005; Carballedo et al. 2011; Costafreda et al. 2013; Demenescu et al. 2013; Kim et al. 2011) have been found in stress-related disorders, and have been considered indicative of impaired emotional modulation. In parallel to the reported amygdala-OFC connectivity, our results point to an increased amygdala-ACC coupling in T homozygotes, however, only at an uncorrected level (depicted in Online Resource 7). Thus future studies including patients should examine whether amygdala-ACC connectivity is altered as a function of *FKBP5* genotype.

In the present study, an effect of *FKBP5* was obtained in the left amygdala activity and volume and an interaction effect with EN on right amygdala activity. So far, there is no explanation as to why these *FKBP5* effects were lateralized, as findings of lateralization of amygdala activation and volume remain inconclusive. For example, PTSD patients were found to show more pronounced hyperactivity in the left than in the right amygdala when confronted with trauma-related words (Protopopescu et al. 2005) or masked fearful faces (Rauch et al. 2000). However, this lateralized effect was not confirmed in a meta-analysis (Etkin and Wager 2007). Likewise, Lorenzetti et al. (2010) found larger left but not right amygdala volumes in remitted depressive patients, indicative of vulnerability as well as a state marker of depression. Lateralization of the amygdala has long been a matter of discussion (Baas et al. 2004; Sergerie et al. 2008) and awaits further investigation in the context of psychopathology.

Several limitations of our study have to be considered when evaluating the results. First, the sample size is relatively small for a genetic association study, albeit in accordance with other recent studies (White et al. 2012) and with previous estimates of necessary samples for imaging genetic studies of common functional variants (Mier et al. 2010). Second, we did not collect endocrine data which would have made it possible to draw the connection between central and peripheral effect of *FKBP5*. Third, with regard to the adversity measures, one has to consider that, in our sample, only a small number of subjects reported having experienced severe maltreatment. Thus, we were unable to investigate G × E related to abuse, as variation in the respective CTQ subscale was markedly restricted. Further longitudinal studies with children at risk are warranted to clarify whether the observed heightened amygdala activity is specific to the interaction with EN. Moreover, the prospective measure used in this study to ascertain objective information on childhood adversity did not specifically address childhood maltreatment, but rather pertained to a stressful family

environment which might foster maltreatment. Fourth, we cannot rule out the possibility that the observed genotype and G × E effects are due to a polymorphism in linkage disequilibrium with the one investigated. However, when considering the results of White et al. (2012), who genotyped several functional polymorphisms in *FKBP5*, rs1360780 showed the greatest interaction effects on amygdala activity.

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Conflict of interest TB served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, Otsuka, Oxford outcomes, PCM scientific, Shire and Viforpharma. He received conference attendance support and conference support or received speaker's fee by Lilly, Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Lilly, Shire & Viforpharma. AML receives consultant fees and travel expenses from AstraZeneca, Hoffmann-La Roche, Lundbeck Foundation, speaker's fees from Pfizer Pharma, Lilly Deutschland, Glaxo SmithKline, Janssen Cilag, Bristol-Myers Squibb, Lundbeck and AstraZeneca. All other authors declare that they have no biomedical financial interest or potential conflicts of interest. The present work is unrelated to the above grants and relationships.

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